## SUPPORT FOR THE AMENDMENTS

Applicants have amended Claims 24, 32, and 39 to incorporate the limitations of claims 29-31, 34-36, and 41-43, respectively. Accordingly, support for amended Claims 24, 32, and 39 can be found in Claims 24, 29-31, 32, 34-36, 39, and 41-43, as previously presented.

No new matter has been added by these amendments. Claims 24-28, 32, 33, 37-40, and 44-48 remain active in this application.

## REMARKS

Present Claims 24-28 and 46 relate to pharmaceutical compositions which comprise:

a corticosteroid;

a hydrofluoroalkane propellant which comprises at least one member selected from the group consisting of 1,1,1,2 –tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and mixtures thereof;

ethanol; and

an antioxidant,

wherein said composition is in the form of a solution and said antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of said composition..

Present Claims 32, 33, 37, 38 and 47 relate to pressurized metered dose inhalers which comprise a container equipped with a metering valve and containing a pressurized aerosol composition comprising:

a corticosteroid;

a hydrofluoroalkane propellant which comprises at least one member selected from

the group consisting of 1,1,1,2 –tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and mixtures thereof;

ethanol; and

an antioxidant,

wherein said composition is in the form of a solution and said antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of the composition.

Present Claims 39, 40, 44, 45, and 48 relate to methods for the treatment of a bronchial disorder comprising administering a pharmaceutical aerosol composition comprising:

a corticosteroid;

a hydrofluoroalkane propellant which comprises at least one member selected from the group consisting of 1,1,1,2 –tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and mixtures thereof;

ethanol; and

an antioxidant,

wherein said composition is in the form of a solution and said antioxidant is present in an amount of 0.2 % to 20% by weight, based on the weight of the composition.

The inventors have discovered that the presently claimed compositions, pressurized metered dose inhalers, and methods are particularly effective for the treatment of bronchial disorders. The cited references contain no disclosure or suggestion of the presently claimed compositions, pressurized metered dose inhalers, or methods. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claims 24, 27, 30-32, 35, and 36 under 35 U.S.C. § 102(b) in view of

U.S. Patent No. 2,868,691 (Porush et al.) has been obviated by amendment. As the Examiner will note, Claims 24 and 32 have been amended to incorporate the limitations of Claims 29 and 34, respectively. Applicants submit that amended Claims 24 and 32 are not anticipated by Porush et al. for the same reasons that Claims 29 and 34 were not rejected as being anticipated by this reference. In addition, Applicants submit that Porush et al. cannot make present Claims 24, 27, 30-32, 35, and 36 for the following reasons.

Porush et al. discloses a self-propelling composition comprising a medicament dissolved in a liquid propellant which is a fluorinated or fluoro-chlorinated lower aliphatic hydrocarbon, preferably with the aid of a co-solvent (*see*, column 1, lines 62-67). The propellant in Porush et al. is preferably a halogenated lower alkane, examples of which are listed in column 2, lines 6 - 27. Particularly suitable propellants are dichlorodifluoromethane (Freon 12), trichloromonofluoromethane (Freon 11), dichlorotetrafluoroethane (Freon 114) and their mixtures (*see*, column 2, lines 16-27). ***Therefore, Porush et al. is only concerned with the old CFC propellants.***

Porush et al. discloses that the medicament employed in the composition can be one which is therapeutically effective when administered by inhalation and which may be brought into stable solution ***in any of the above defined liquified propellants***, if necessary, with the aid of a co-solvent ***and/or stabilizing substance*** (*see*, column 2, lines 41-27).

Therefore, the medicament used in the composition must be dissolved in the above defined propellant. A list of possible medicament is given in column 2, lines 46-60. A corticosteroid, *i.e.*, cortisone, appears on line 59, among various options of medicaments.

A co-solvent, a stabilizing substance or a mixture thereof can be employed to dissolve the medicament. In other words, ***the stabilizer is not a necessary component*** in the

compositions of Porush et al. as clearly stated in column 3, line 74, ***"A stabilizer, if desired, is added".***

The co-solvent may be any liquid substance which assists in dissolving the medicament in the liquid propellant (*see*, column 2, lines 61- 65). Examples of co-solvents include non-toxic lower alcohol and ethers, *e. g.*, ethanol, diethyl ether, chloroform, mixtures of ethanol and water, and mixtures of chloroform and ethanol (*see*, column 3, lines 4-7). The stabilizers of Porush et al. include alkali-metal ascorbates, ascorbic acid, butylated hydroxytoluene, and butylated hydroxyanisole (*see*, column 3, lines 11-15).

In summary, Porush et al. is concerned with a different propellant and does not provide any teaching of either the choice of ethanol as the co-solvent or the inclusion of an antioxidant as a further essential ingredient of the composition.

Moreover, one of the important features of the compositions of Porush et al. is the fact that the ***components of the compositions must be present within certain critical proportions, as otherwise the benefits of the invention are not obtained*** (*see*, column 3, lines 18 – 21 ). Porush et al. disclose, in this respect, and as far as the stabilizer is concerned, ***"It is normally not necessary to employ a stabilizer in an amount in excess of 0.25% by weight of the composition"*** (*see*, column 3, lines 15-17).

Consequently, the claimed composition of the present invention is novel over Porush et al. in view of the presence of an HFA propellant system and ethanol in which an antioxidant is added in the well defined amount of 0.2 % to 20% by weight. Certainly, this reference cannot make Claims 46-48 obvious, as these claims require "wherein said antioxidant is present in an amount of 1% to 2% by weight, based on the weight of the composition."

Turning to the examples of Porush et al., it seen that all the compositions are based on CFC propellants. Moreover, the co-solvent can be indifferently ethanol, an ether, a mixture of ethanol and water or a mixture of chloroform and ethanol.

The only composition of Porush et al. which contains ethanol as the co-solvent and an antioxidant, *i.e.*, ascorbic acid, is the composition of example 3 which further contains the additional component, hydrochloric acid. Moreover, the ascorbic acid is present in the very low amount of only 0.15% by weight, based on the weight of the composition, which is less than the amount required by the present claims, 0.2 % to 20% by weight. Further, none of the exemplified compositions of Porush et al. contains a corticosteroid as the medicament.

The technical problem addressed in Porush et al. is to provide a stable therapeutic composition which contains a liquefied non-toxic propellant material (*see*, column 1, lines 53-55). The composition of Porush et al. is in form of a solution and a co-solvent may help in dissolving the medicament in the propellant. Porush et al. discloses that a stabilizer can be used either as a replacement for the cosolvent or in addition to the cosolvent, in this latter case in an amount no higher than 0.25% by weight on the weight of the composition (see, column 3, lines 15-17).

In sharp contrast, the problem to be solved by the present invention lies in the provision of an aerosol composition of a ***corticosteroid*** in the form of a solution in ***an HFA propellant*** and ***ethanol*** as a cosolvent, with similar characteristics to the previous CFC propellant based compositions, which they replace (*see, e.g.*, page 8, lines 12-17 of the specification). The solution provided by the present claims involves the ***addition of an antioxidant*** as a low volatility component in the specific range of between 0.2% and 20% by weight, based on the weight of the composition.

As explained in the present specification, the old chlorofluorocarbon propellants had properties particularly suitable for use in aerosols, including high vapour pressure which generated clouds of droplets of a suitable particle size from the inhaler (*see*, page 2, lines 3-6). However, the CFC propellants have been implicated in the destruction of the ozone layer and their use is to be discontinued.

On the other hand, as reported in K. J. McDonald, et al., International Journal of Pharmaceutics, vol. 201, pp. 89-107 (2000) (McDonald et al.) (copy attached hereto as Exhibit A), the safer new HFA propellants and the old CFC propellants possess quite different physical and chemical properties (*see*, Table 4 on page 94). In particular, the boiling points and vapour pressures of the CFC and HFA propellants differ significantly (*see*, Table 4). The vapor pressure of the propellant is an important parameter of a MDI system, since it determines the speed and rate of evaporation and, in turn, the aerosol droplet size and efficiency of deposition within the lung (*see*, McDonald et al., page 93, right column, item 2.3, second paragraph).

The present inventors have found that the addition of an antioxidant, as a low volatility component, to the composition, allows the design of formulae which contain an HFA propellant and which afford an aerosol with similar particle size characteristics to those of the old CFC formulations they replace. This also permits development of products which are pharmaceutically and clinically equivalent to the CFC formulations (*see*, page 8, lines 25-29, of the present specification).

On the other hand, the low vapour pressure of the low volatility component is to be contrasted with that of the cosolvent, which is ethanol (*see*, from page 11, line 29, to page 12, line 7, of the present specification). The presence of an antioxidant in a well defined amount,

in combination with ethanol as the co-solvent and an HFA propellant, are the technical features specifically required by the present claims.

By adding an antioxidant to the composition, the present inventionprovides a solution both for the problem of the stability of the formulation and to the therapeutic problem associated with the new medicinal aerosols, as the presence of the antioxidant in the amount of at least 0.2% influences the size of the particles (*see*, page 11, lines 6-12, and page 13, lines 20-21, of the present specification).

The differences between the old and the new propellants were well known to those skilled in the art at the time the application was filed. Therefore, one of skill in the art would not have turned to Porush et al., which deals with a CFC formulation, to solve the problems associated with the new propellants. Therefore, there would have been no motivation for the skilled artisan to look at Porush et al.

In summary, Porush et al. provides no disclosure or suggestion of the presently claimed composition or of its benefits. There is no disclosure in this reference of a composition which would contain an antioxidant in the specific amount of 0.2 to 20% w/w, in combination with ethanol and an HFA propellant in order to provide a composition which is not only stable, but also provides an aerosol with particle size characteristics similar to those of the CFC-propellant compositions. In fact, there is nothing in this reference which would even remotely suggest that the addition of an antioxidant would influence the particle size of the composition on actuation of the inhaler.

For these reasons, Porush et al. also cannot make the present claims obvious.

Accordingly, the rejection should be withdrawn.

The rejection of Claims 28, 29, 33, 34, and 39-43 under 35 U.S.C. § 103(a) in view of

Porush et al. in view of U.S. Patent No. 5,776,433 (Tzou et al.) is respectfully traversed. Tzou et al. has been discussed in detail in the previously filed response. Simply put, there is nothing in Tzou et al. which can cure the basic deficiencies of Porush et al.

As already explained, Tzou et al. discloses aerosol compositions which contain flunisolide, ethanol, and HFA propellants and that certain excipients, *e.g.*, certain surfactants, flavoring agents, and/or water are beneficial to the chemical stability of certain formulations. Tzou et al. also disclose that flunisolide had been previously provided in the form of a nasal formulation in an ***aqueous*** solution of propylene, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride.

In spite of this, there is nothing in Tzou et al. which would even remotely suggest adding an antioxidant to an HFA propellant formulation. Moreover, there is nothing in Tzou et al. which would even remotely suggest that the addition of an antioxidant to an HFA propellant formulation would have any effect of the properties of the aerosol formed from that composition.

Therefore, there would have been no reasons for one of ordinary skill, in absence of any hint, to specifically select the antioxidant from the various ingredient of the aqueous formulation mentioned in passing by Tzou et al. and combine it with the teaching of Porush et al., which is directed to a completely different composition (based on CFC propellants), to arrive at the presently claimed compositions.

For these reasons, the rejection is improper and should be withdrawn.

The rejection of Claims 25, 26, 37, 38, and 44-48 under 35 U.S.C. § 103(a) in view of Porush et al. in view of U.S. Patent No. 4,584,320 (Rubin) is respectfully traversed. Applicants submit that there is nothing in Rubin which can overcome the deficiencies of

Porush et al. As already pointed out, Rubin is concerned with ***suspension formulations in the old CFC propellants***. Moreover, the formulations of Rubin do not contain a co-solvent.

In the Office Action, the position is taken that antioxidants are recognized in the art and one of ordinary skill would have been able to select any one of said antioxidant for a formulation whether a solution or a suspension. It is asserted that the same antioxidants would perform their function in any formulation.

However, Applicants respectfully submit that in the presently claimed compositions which exist in form of a solution in the specific HFA propellant/ethanol system, the antioxidant performs the specific function of modulating the vapor pressure of the solution to influence the size of the liquid aerosol particles delivered on actuation of the inhaler.

There is no teaching of this function in any of the cited references. Moreover, this function could not have been derived from a suspension formulation in a different propellant system, and in absence of a cosolvent, ***wherein the medicament is in solid form and the size of the particles is predetermined by the micronisation process.***

Moreover, as already explained, extensive testing has been required in reformulating products to replace the CFC MDIs, due to the different physico-chemical properties of the new HFA propellants. Thus, starting form the teachings of the cited prior art, taken alone or in combination, those skilled in the art would have had no expectation of obtaining the benefits provided by the presently claimed compositions. ***Specifically, one of skill in the art would have had no expectation that the addition of a well defined amount of an antioxidant as a low volatility component would allow the modulation of the size of the liquid particles delivered on actuation of the inhaler, to provide aerosol compositions in the form of solution based on an HFA propellant which have similar characteristics of the old***

***CFC compositions which they replace (see, at page 8, lines 1-19 and 25-29).*** In this respect, the specific claimed ranges of the antioxidant and the specific HFA propellant/ethanol mixture are equally important in regard to modulating the vapor pressure of the solution.

Once again, the rejection is improper and should be withdrawn.

Applicants submit that the present application is in condition for allowance, and early notice to this effect is earnestly solicited.

Applicants respectfully request that, if any matters which would preclude the allowance of this application remain, the Examiner call Applicants' undersigned representative to resolve such matters prior to the next written communication from the PTO.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220

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# Transition to CFC-free metered dose inhalers — into the new millennium

Keith J. McDonald [a,*], Gary P. Martin [b]

[a] *Medicines Control Agency, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ, UK*

[b] *Department of Pharmacy, King's College London, Franklin-Williams Building, 150 Stamford Street, London SE1 8WA, UK*

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**Abstract**

Metered dose inhalers (MDIs) are the most popular vehicle for drug delivery into the lungs and some 500 million are manufactured each year. All MDIs marketed prior to 1995 contained chlorofluorocarbons (CFC) as a propellant. These are implicated in the depletion of stratospheric ozone and, except for specific exemptions, their production has been banned since 1996 under the terms of the Montreal Protocol. Hydrofluoroalkanes have been identified as suitable alternatives for MDI propellants but their physico-chemical properties differ significantly from CFCs and an extensive redevelopment and testing programme has been required to demonstrate the safety, quality and efficacy of HFA containing MDIs. Hydrofluoroalkanes contribute to global warming but the benefit to human health through continued MDI availability currently outweighs the environmental concern. Several HFA-MDIs have reached the market and the transition to replace existing CFC-MDIs is now underway. © 2000 Elsevier Science B.V. All rights reserved.

*Keywords:* Metered dose inhalers; Chlorofluorocarbons; Hydrofluoroalkanes

## 1. Introduction

Delivery of drugs directly to the lower respiratory tract by aerosol inhalation in the treatment of asthma and other respiratory diseases, is well established and enshrined in relevant national and international guidelines (British Thoracic Society et al., 1993; National Heart, Lung and Blood Institute, 1995). The drug is delivered in close proximity to its intended site of action, resulting in rapid response. By-pass of the gastro-intestinal tract also eliminates absorption and metabolic variability associated with the route, permitting relative dose reduction and optimisation of the risk:benefit ratio.

Metered dose inhalers (MDIs) were first introduced into clinical practice for treatment of the symptoms of asthma and chronic obstructive pulmonary disease (COPD) in the 1950s by Riker Laboratories. The MDI is a convenient dose delivery system that is well liked by patients and prescribers and is less expensive than other respiratory delivery systems. About 80% of inhalation therapies in the world's largest patient

* Corresponding author.

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populations are delivered by MDI (International Pharmaceutical Aerosol Consortium, 1997). In the UK alone, 39 million MDIs are used each year (Department of the Environment, Transport and the Regions, 1999) and annual world-wide production runs to about 500 million devices (Tansey, 1997a).

Despite this popularity, optimal dose delivery is dependent on patient technique and an ability to co-ordinate the actuation of the dose with inspiration of air into the lungs.

Incorrect use of MDIs has been reported to run to about 38% of users and, in spite of its obvious popularity, this mode of drug delivery may be unsuitable for some individuals (McFadden, 1995).

The alternatives are dry powder inhaler (DPI) and nebuliser which, like the MDI, enable delivery of a fraction of the equivalent oral dose of drug for the same therapeutic effect. Both of these devices have significant disadvantages that hinder wider utilisation. The dose delivered by DPI varies with age, gender, disease state and breathing cycle (Smith and Bernstein, 1996) and they are not suitable for all patient groups, especially very young children. Recent developments have seen the introduction of a variety of more user friendly multi-dose devices (Prime et al., 1997) and these have resulted in an increase in use of DPI products. However, the overall use of inhaled products has also grown and wider DPI use has not had a significant impact on MDI sales (Official Journal of the European Communities, 1998).

The nebuliser has not yet been produced in a convenient form for everyday use and current use is dominated by particular patient groups such as infants, patients with severe disease and those requiring higher doses of drug. Development of a portable reusable pocket-sized nebuliser system is underway (Hickey and Dunbar, 1997) but it is unlikely to be cost effective as a general replacement for MDIs.

In spite of the improved delivery efficiency of the respiratory route in comparison to oral administration, there are opportunities to improve drug targetting and reduce the dose still further. Less than 30% of the dose from a MDI or DPI reaches the lung and most of the remainder impacts on the oro-pharynx, with a smaller proportion retained within the mouthpiece of the actuator (Hickey and Dunbar, 1997). Some reformulated metered dose inhalers have been designed to improve the proportion of drug delivered into the lungs with consequent dose reduction compared to earlier products containing CFC propellants (Leach, 1998).

### *1.1. Respiratory disease*

Incidence of asthma is estimated to be around 5–8% of the population in the developed world and the number of asthma sufferers world-wide amount to about 300 million people. Diagnosis of the disease is increasing at about 5% per year and it is the most frequently reported chronic condition among UK children. Asthma is responsible for the death of about 1700 people each year in the UK (International Pharmaceutical Aerosol Consortium, 1997; Official Journal of the European Communities, 1998).

The prevalence of chronic obstructive airways disease (COPD) has been estimated at around 8–15% of the general population and together with asthma, the two diseases comprise the third most common causes of death in the European Union (International Pharmaceutical Aerosol Consortium, 1997).

The demand for effective treatments for respiratory conditions therefore continues to grow into the new millennium. The range of drugs administered by inhalation is currently dominated by those intended for local pulmonary action. Advances in biotechnology have also stimulated interest in this route for drugs intended for systemic action. Respiratory delivery of acid or enzyme labile materials such as insulin, deoxyribonuclease, influenza vaccine and gene replacement therapy have been developed and the potential of this route for systemic treatment of other conditions remains to be fully realised.

### *1.2. Environment*

Until 1995, all marketed MDIs contained chlorofluorocarbons (CFC) as the delivery propellant. CFC have been more extensively used for other

domestic and industrial purposes as a result of their chemical stability and low toxicity, however, concern over the possible detrimental effect of CFC to the ozone layer was first raised in the 1970s (Molina and Rowland, 1974). Since this time, the causal role of CFC in ozone layer thinning has gained support culminating in the signing of the Montreal Protocol on Substances That Deplete the Ozone Layer in 1987, which committed the signatory nations (now over 150) to cease production of CFC by 1996 (Montreal Protocol, 1987. Specific exemptions were granted for defined essential uses where there were no technologically or economically viable alternatives to CFCs and these included MDI production. Exemptions are issued on an annual basis and the pharmaceutical industry was faced with the prospect of diminishing, expensive supply and the possibility of being left behind by the first competitor to pioneer an equally popular alternative. In recognition of the popularity of this form of delivery, pharmaceutical aerosol manufacturers have committed large resources to the development of CFC-free MDI systems.

CFCs contribute both to the depletion of the ozone layer and to the greenhouse effect. The mechanism of ozone depletion is proposed to be via unbalancing of the stratospheric ozone formation and depletion equilibrium. Ozone is degraded to molecular oxygen plus free radical with the absorption of UV B radiation (Fig. 1).

The radicals formed may combine together to form molecular oxygen or with existing molecular

$$O_2 \xrightarrow{h\nu} 2O\bullet$$

$$O_2 + O\bullet \longrightarrow O_3$$

$$O_3 \xrightarrow{h\nu} O_2 + O\bullet$$

$$O_3 + O\bullet \longrightarrow 2O_2$$

Fig. 1. Proposed stratospheric oxygen/ozone equilibrium (Noakes, 1995).

$$O_3 + Cl\bullet \longrightarrow ClO\bullet + O_2$$

$$ClO\bullet + O_3 \longrightarrow 2O_2 + Cl\bullet$$

$$Cl\bullet + Cl\bullet \longrightarrow Cl_2$$

Fig. 2. Proposed halogen disruption of stratospheric oxygen/ozone equilibrium (Noakes, 1995)

oxygen to re-form ozone. CFC emissions pass directly into the upper atmosphere where they are retained until degraded by ultra-violet radiation releasing highly reactive chlorine radicals. Chlorine radicals catalyse the breakdown of ozone to molecular oxygen without the absorption of ultra-violet radiation or generation of oxygen radicals. One chlorine atom may be repeatedly recycled catalysing thousands of reactions prior to formation of molecular chlorine (Molina and Rowland, 1974) and more ultra-violet radiation is therefore transmitted to the surface of the Earth (Fig. 2).

Confirmation of stratospheric ozone depletion was first reported over the Antarctic in 1985 (Farman et al., 1985) and now occurs annually. Depletion of up to 40% of stratospheric ozone has been recorded in each year since 1995 over Northern Europe (Official Journal of the European Communities, 1998).

The consequences of ozone depletion for humans could manifest as increased incidence of skin cancer, eye damage and premature ageing of skin, while effects on the food chain and climate changes could adversely affect all life forms on the planet. The additional lifetime risk of skin cancer in children living in the UK today is predicted to increase by 4–10% if ozone depletion continues at the current rate (The Potential Effects of Ozone Depletion in the United Kingdom, 1996).

The problem is exacerbated by the stability of CFC in the upper atmosphere, with residence times of up to 200 years, leaving the burden of today's emissions with future generations.

### *1.3. The Montreal Protocol*

The Montreal Protocol defines the circumstances permitting 'essential' use exemptions as;

Table 1
CFC approved by the Parties to the Montreal Protocol in the European Community, 1996 1999

| Year | Tonnes of CFC |
|---|---|
| 1996 | 7546 |
| 1997 | 6635 |
| 1998 | 5610 |
| 1999 | 5000 |

1. It is necessary for the health, safety or is crucial for the functioning of society (encompassing cultural and intellectual aspects).
2. There are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health.

Essential use applications are considered by the Technology and Economic Assessment Panel (TEAP) of the United Nations Environment Programme (UNEP) and criteria for essential use exemption have been defined as:

1. All economically feasible steps have been taken to minimise the essential use and any associated emissions of the controlled substance.
2. The controlled substance is not available in sufficient quantity and quality from existing stocks of banked or recycled controlled substances, also bearing in mind the developing countries' need for controlled substances.

Essential use status is considered every 2 years and requests for CFC for use in manufacture of MDIs are reviewed annually.

In the European Union, requests for CFCs for manufacture of MDIs are submitted to the Parties to the Montreal Protocol by the European Commission on behalf of Member States. Each manufacturer applies to the European Commission for authorisation to use a specified quantity of CFCs for the manufacture of MDIs. A management committee composed of representatives of the member states advises the European Commission on the quantities of CFCs to be allocated to each producer.

The quotas of CFC approved for use in the manufacture of MDIs in the European Community are indicated in Table 1.

This compares with over 400 000 tonnes of CFC produced for all industrial purposes in the USA alone in 1974 (Howard and Hanchett, 1975).

## 2. The metered dose inhaler

The device conventionally consists of five components which have an interdependent effect on drug delivery. These are; the drug substance, the canister, the propellant/excipient mixture, the metering valve and the actuator. The other significant factors on efficacy of drug delivery are patient technique and lung pathology.

Desirable functions of the MDI can be considered to be:

- Accurate and reproducible dosing.
- Efficient atomisation of the aerosol to deliver the drug to the required site.
- Retention of pressurised components.
- Protection of contents from external ingress.
- Convenient dimensions for user handling and portability.
- Multiple dose device ideally including an indicator of dose availability.
- Co-ordination of dose actuation with breath inspiration.
- Acceptable organoleptic properties.

Replacement of the propellant cannot be considered in isolation and implications for the MDI device are considered in the following discussion.

### 2.1. Aerosol propellants

In the absence of a new technology for respiratory drug delivery, the search for possible replacements for CFC for MDI was defined in terms of toxicity, flammability, chemical stability, physical properties and environmental compatibility. The template for these properties, with the exception of environmental suitability, were the existing MDI propellants, CFC 11, 12 and 114, which had been used safely and effectively for many years (Table 2). The candidates that emerged were hydrofluoroalkanes (HFA). Specifically, tetrafluoroethane (HFA 134a) and heptafluoropropane (HFA 227) were recognised as potentially suitable MDI propellants. These

Table 2
CFC and HFA propellants — nomenclature

| Code name | Chemical name | Chemical structure |
|---|---|---|
| CFC 11 | Trichlorofluoromethane | $CCl_3F$ |
| CFC 12 | Dichlorodi-fluoromethane | $CCl_2F_2$ |
| CFC 114 | Dichlorote-trafluorocthane | $C_2Cl_2F_4$ |
| HFA 134a | Tetrafluoroethane | $C_2H_2F_4$ |
| HFA 227 | Heptafluoropropane | $C_3HF_7$ |

were non-flammable, non-ozone depleting, chemically stable propellants with suitable vapour pressures for MDI use.

Hydrofluoroalkanes contribute to the greenhouse effect but to a lesser extent than CFC (Table 3). It has been estimated that HFA from MDIs will contribute less than 0.1% of total world-wide greenhouse gas emission by 2005 (International Pharmaceutical Aerosol Consortium, 1997).

A further concern is the accumulation of trifluoroacetic acid, a breakdown product of HFA-134a, in wetland areas (Snell, 1995). The environmental effects of HFA are therefore not completely benign but the ozone depletion problem has demanded swift action. Development of HFA for MDI propellants is currently justified in balancing medical need against their environmental impact.

### 2.2. Propellant toxicity

Toxicity and environmental suitability of hydrofluoroalkanes were investigated initially in collaborative studies by chemical companies with an interest in their development. The Programme for Alternative Fluorocarbon Toxicity Testing (PAFT) commenced the toxicological and environmental screening of hydrofluoroalkanes and hydrochlorofluoroalkanes for industrial replacement of CFC propellants in 1987. This was followed in 1988 by the Alternative Fluorocarbons Environmental Acceptability Study (AFEAS) which investigated the environmental impact of potential CFC replacements. Further toxicology testing to meet the exacting requirements for medicinal products was conducted by the pharmaceutical industry. Collaborative International Pharmaceutical Consortia for Toxicology (IPACT) investigated the safety of these new propellants for respiratory delivery to humans in order to satisfy world-wide regulatory authorities. In Europe, the Committee for Proprietary Medicinal Products endorsed the suitability of HFA 134a and HFA 227 as propellants for administration into the lungs in its statements of 1994 and 1995, respectively(Committee for Proprietary Medicinal Products, 1994, 1995).

### 2.3. Physico-chemical properties of aerosol propellants

HFA and CFC propellants possess quite different physical and chemical properties (Table 4).

The vapour pressure of the MDI system determines the speed and rate of evaporation and, in turn, the aerosol droplet size and efficiency of deposition within the lung. High vapour pressure will provide small droplets due to rapid propellant evaporation but the velocity of plume discharge can result in large percentage of emitted dose impacting in the oro-pharynx (Polli et al., 1969;

Table 3
Environmental impact of MDI propellants (Smith, 1995)

| Propellant | Ozone depletion potential | Atmospheric life (years) | Global warming potential[a] |
|---|---|---|---|
| CFC 11 | 1 | 60 | 1 |
| CFC 12 | 1 | 125 | 3 |
| CFC 114 | 0.7 | 200 | 3.9 |
| HFA 134a | 0 | 16 | 0.3 |
| HFA 227 | 0 | 33 | 0.7 |

[a] Relative to CFC 11.

Table 4
Physico-chemical properties of MDI propellants (June and Ross, 1995; Tiwari et al., 1998a)

| Propellant | Liquid density (g/ml) | Liquid viscosity (mPas) | BP (°C) | VP (psig at 20°C) |
|---|---|---|---|---|
| CFC 11 | 1.49 | 0.43 | 23.7 | −1.8 |
| CFC 12 | 1.33 | 0.22 | −29.8 | 67.6 |
| CFC 114 | 1.47 | 0.36 | 3.6 | 11.9 |
| HFA 134a | 1.21 | 0.22 | −26.5 | 68.4 |
| HFA 227 | 1.41 | 0.26[a] | −17.3 | 56.0 |

[a] Solvay Fluor und Derivate GmbH, Hanover, Germany.

Gonda, 1992; Harnor et al., 1993). Dalton's Law permits the total vapour pressure of a system to be determined by the sum of the partial pressures of its components and Raoult's Law provides for the calculation of the partial pressure of those components in the system. These have been used to design CFC propellant blends to achieve a suitable vapour pressure for lung deposition (Dalby et al., 1996).

The boiling points and vapour pressures of CFC and HFA propellants differ significantly (Table 4). The formulator of MDI using HFA propellants is potentially restrained by being unable to mix propellants with significantly differing vapour pressures to obtain desired lung deposition. That said, linear increase in vapour pressure of HFA-134a and HFA-227 blends with proportional increase in HFA-134a and compliance with Raoult's Law over a temperature ranges of 6–42°C have been reported (Williams and Liu, 1998), but there remains less flexibility to vary the system vapour pressure by blending different HFA propellants compared with the possibilities afforded using CFC propellants. The vapour pressure of HFA MDIs is likely to be higher unless other low volatility components such as ethanol are included.

The propellant boiling point impacts on the method of filling of the canisters. CFC 11 permitted preparation of the formulation as liquid at room temperature, filling and crimping the valve on to vial before adding the other propellants under pressure or low temperature via the valve. New processing routes for MDI containing HFA propellants have been required in order to liquefy the propellant (Smith, 1995).

The solvency properties of HFA propellants also differ from the CFC predecessors. Partial solubility of suspended drug substance in the dispersant may result in crystal growth, poor physical stability and unacceptable product performance. Surfactant solubility is very much reduced in HFAs with further implications for the physical stability of the system. The function of elastomeric components within valves and the profile of extractables released from these components are also influenced by the solvency properties of the propellant (Smith, 1995).

The capacity for CFC and HFA propellants to support microbial growth has been compared (Meier et al., 1996). Bactericidal properties of HFA 134a against *Staphylococcus aureus* are comparable to CFC blends whereas HFA 227 is bacteriostatic. *Bacillus subtilis* spores will survive in both CFC and HFA propellants. The authors conclude that testing of the microbial quality of MDIs containing HFA propellant should include a test of total viable aerobes in recognition of spore survival. They propose a tighter acceptance limit of ten bacteria per gram or millilitre as compared with the limit currently included in the European Pharmacopoeia (1997). They also argue that the Ph. Eur. test for absence of *S. aureus* is unnecessary as the organism does not survive in HFA 134a or proliferate in HFA 227.

### 2.4. Performance testing of reformulated MDIs

In reformulating products to replace the CFC MDIs, manufacturers have had to consider whether their objective should be therapeutic equivalence with the original CFC containing products or to improve the performance of the

new products. Characterisation of the aerodynamic particle size distribution of test and reference products is critical in this development. These data can be rationally used in the development and selection of products for further investigation of deposition in volunteers or patients and, where appropriate, pharmacokinetic studies. Ultimately pharmacodynamic and/or clinical studies will be required to demonstrate equivalence to existing CFC-MDI or, where there are changes to the dosage regimen, efficacy and safety of the reformulated product (Rogers and Ganderton, 1995).

### 2.5. Determination of aerodynamic particle size

The aerodynamic size of the drug particle or droplet in the emitted aerosol determines the degree of deposition within the lung, the respirable (or fine particle) fraction and reflects the delivery efficiency of the system (Hickey, 1992). Deposition of a low percentage of the emitted dose within the lung leaves the residual deposited in the oro-pharynx, with increased probability of local and systemic side effects. The aerodynamic size is defined as the diameter of a sphere of unit density with the same settling velocity as the particle. This term takes account of particle size, density and shape, all of which influence the deposition pattern. Drug particle hygroscopicity and charge may also be significant and patient technique, inspiratory rate and volume and the disease state are further contributory variables (Padfield, 1987).

Aerosolised drug deposits in the lung by sedimentation, inertial impaction and Brownian motion (Hallworth, 1987). The momentum of large particles within the inspired airstream favours their early deposition in the bifurcating, narrowing airway system. Particles in excess of 10 μm will deposit in the oro-pharynx and are unlikely to reach the lungs. Those of diameter less than 1 μm deposit principally by Brownian motion. The tidal nature of respiration mitigates against significant drug deposition by Brownian motion and very small particles are exhaled before collision with the endothelium. The optimal size range for drug deposition is in the range 1–5 μm and has generally been defined as the respirable dose (Hickey, 1992). This terminology has been challenged on the basis that it infers a 1:1 correlation with the dose deposited in vivo and the alternative term, fine particle fraction (or dose), is proposed (Clark et al., 1998). It is also argued that an in vitro size range of 1–3 μm is more clinically relevant (Newhouse, 1998). By whatever name, this definition takes no account of site of deposition within the lung and the desirable aerodynamic size range for a product intended for systemic effect may therefore differ from another for local action on the smooth muscle within the lung.

Definition of a rapid, usable and predictive in vitro method is complicated by the dynamic nature of the aerosol with flash evaporation of propellant, decreasing droplet size and deceleration of the aerosol plume over distance, in addition to the complexity of the anatomy and physiology of the lung.

A number of different methods, based on different physical principles, can be used to characterise the aerosol size but results obtained from different methods will not be readily comparable (Tiwari et al., 1998a). Information on the real time dynamics of the aerosol plume is obtained by optical methods such as laser diffraction (Ranucci, 1992), holography (Gorman and Carroll, 1993), phase Doppler anenometry (Ranucci and Chen, 1993), time of flight spectroscopy (Niven, 1993) and right angle light scattering (Jager et al., 1993). These permit effects of formulation variables such as actuator and spacer design on the changing velocity and shape in the emitted plume but do not take account of respiratory tract tortuosity and the aerodynamic behaviour of the particles (Timsina et al., 1994).

Inertial impactors have been developed from instruments designed for microbial sampling of air to provide detailed information on the size, distribution and mass of the fine particle fraction of pharmaceutical aerosols. The sampling chamber of these devices is designed to approximate the human throat and the method of collection of the different size fractions of aerosol within the device bears similarities to the respiratory tract. Namely, that a particle suspended in a moving airstream will impact on an intervening surface when its inertia overcomes the drag forces tending

to retain it in the airstream (Milosovich, 1992). The largest particles impact on the initial stages and smaller particles are carried further through the instrument. An absolute filter is used to collect any fines. The collection medium may be liquid or a solid surface.

Particle size information is commonly expressed as median mass aerosol diameter (MMAD) and the spread of data as the geometric standard deviation (GSD). The distribution by mass or percentage of dose above the each pre-calibrated cut-off stage of the equipment provides useful comparative data between formulations.

The mass on each of the impactor stages does not correspond exactly with the ranges indicated by the manufacturers calibration and data may require inversion to ascertain the true size fractions (Cooper, 1993). Inversion is not usually conducted if the impactor is used for comparative studies of formulation or device variables but must be considered where studies are conducted using different impactor models and for prediction of deposition within the respiratory tract (Marple et al., 1998).

Data obtained can be variable within (Stein and Olson, 1997) and between (LeBelle et al., 1997) impactor models and will vary with sampling chamber dimensions (Aiache et al., 1993), carrier gas flow rate and single or multiple actuation of the device (Graham et al., 1995).

Less detailed information may be required for routine quality control after appropriate characterisation using the impactor method described above and on definition of product and manufacturing variables. Impinger methods have been included in the British Pharmacopoeia since 1988 for this purpose and have the advantage of simplicity but permit segregation of the aerosol into only two size categories.

The value of in vitro data in product development is dependent on how closely they predict the clinical efficacy of the product. Clinical response is dependent upon the dose and location of deposition relative to the target receptors. Bronchial and pulmonary circulation may also contribute to the delivery of the drug to its site of action. For example, cholinergic receptors are concentrated in the bronchi, while asthma inflammation is diffuse and the optimal aerodynamic characteristics may therefore differ for anticholinergic and steroid aerosols. Variation between patient populations must also be considered, for example in infants and children where aerosol deposition efficiency (for particles less than 3 μm) is less than adults (Chua et al., 1994). Deposition is further influenced by rate and volume of inspiration, hold time, airway calibre and variation in the lung and pulmonary parenchymal disease (Newhouse, 1998). The challenge for the in vitro method is considerable but correlations have been demonstrated between these methods and therapeutic effect for particular drugs (Meakin and Stroud, 1983; Padfield et al., 1983; Martonen and Katz, 1993). That said, no generally applicable correlation has been developed and in vitro methods alone are not yet acceptable as surrogates for clinical performance (Rogers and Ganderton, 1995).

### 2.6. Physical nature of the drug substance

Metered dose inhalers are formulated both as suspension and solution of drug in the propellant, depending on the solubility of the active substance in the propellant–excipient mixture. Suspensions have the advantage of chemical stability and delivery of greater mass per unit volume than solutions but have to be carefully formulated so that the physical stability is controlled throughout their lifetime. The potential for crystal growth, solvate formation or polymorph interconversion must be fully addressed early in the formulation development (Byron, 1992). The concentration of the suspension, method of micronisation and particle size distribution of micronised drug will influence the spray characteristics of the product (Gonda, 1985; Chan and Gonda, 1988; Ward and Schultz, 1995).

Aggregation of the finely divided solid phase with resultant sedimentation or creaming as a result of density differences between disperse phase and propellant, manifest as poor dose reproducibility and reduction in the fine particle fraction (Hallworth, 1987). Density differences between finely divided solid disperse phase and the liquid phase of the suspension should be min-

imised in order to promote the physical stability of the suspension and the resulting dose reproducibility.

Optimisation of physical stability and aerodynamic performance of a triamcinolone acetonide suspension MDI (including ethanol) by variation in the relative composition of a mixture of HFA 134a and 227 propellants has been recently demonstrated (Williams et al., 1998). Blending the propellants so that the density of the mixture approached that of the suspended drug improved dose uniformity. This blend also demonstrated the lowest median mass aerodynamic diameter and highest fine particle fraction and performance was maintained on short term storage.

Surfactants have been used to obtain the desired physical stability of the suspension and additionally function as lubricants for the metering valve. The choice of surfactant is limited by toxicological as well as physicochemical considerations, and those used in currently licensed CFC MDI formulations are oleic acid, sorbitan triethanoleate and soya derived lecithin. Surfactants prevent aggregation of the primary drug particles by adsorption onto the solid surface, with the predominant stabilising mechanism being steric repulsion between the projecting hydrophobic chains. Hydrofluoroalkanes are more polar than CFCs and have different and poorly characterised solvency properties (Byron et al., 1994). Solubilities of oleic acid, sorbitan trioleate and lecithin in HFA 134a are in the region 0.005–0.02% w/v (Byron et al., 1994; Dalby et al., 1996). CFC containing MDI formulations have required these surfactants at concentrations of between 0.1 and 2.0% w/w to stabilise the suspension and optimise the function of the metering valve (Atkins et al., 1992). New surfactants that are more soluble in HFA are under investigation. These include polyethylene glycol (PEG), propoxylated PEG and perfluoroalkonic acids but they will not be available until their safety has been demonstrated in chronic respiratory administration (Dalby et al., 1996). The lubricant function of surfactant is not required in newly developed valve systems and this has permitted development of commercial beclomethasone dipropionate (BDP) HFA MDIs without inclusion of surfactant (Snell, 1995). Another approach is to employ a co-solvent to solubilise surfactant in HFA and this may also overcome some of the manufacturing difficulties associated with the absence of a high boiling point replacement for CFC-11 (Tansey, 1997b). Low volatility co-solvents such as ethanol will decrease system vapour pressure and lower the fine particle fraction (Newman et al., 1982). Increasing the ethanol content in solution formulations of BDP in HFA134a decreased the fine particle fraction of BDP and increased actuator and impinger throat deposition (Steckel and Muller, 1998).

Solution formulations of drug in the propellant blend offer the theoretical advantage of improved dose uniformity compared to suspensions. Dose uniformity and aerodynamic size distributions of suspension formulations may vary with storage, orientation and the number of doses fired from the canister (Cyr et al., 1991; LeBelle et al., 1996). Spray characteristics of solution aerosols can also be manipulated by reduction in actuator orifice diameter and by increase in the length of the actuator mouthpiece to produce smaller droplet sizes and deaggregation of suspension particles (Evans et al., 1991; Ranucci et al., 1992; Vervaet and Byron, 1999) but suspensions have the tendency to clog a small diameter orifice.

Significantly greater lung deposition has been demonstrated using MDIs containing experimental solution aerosols compared to suspension aerosol in both healthy and asthmatic patients in scintigraphy studies (Sanders et al., 1997) but these advantages must be balanced against the potential disadvantage of poorer chemical stability of drugs formulated in solutions (Soine et al., 1992), the required concentration of surfactant to stabilise the active substance (Blondino and Byron, 1996) and the toxicological profile of the surfactant. Co-solvents and use of micellar systems to improve drug solubility in CFC propellants, have also been described (Evans and Farr, 1992) but reverse micelle formation has not been observed in HFA 134a (Blondino, 1995 in Vervaet and Byron, 1999).

Propellant solvency properties may necessitate manipulation of the form of the drug substance. Tzou et al., (1997) showed that physical instability

of salbutamol sulphate and base in HFA was correlated with drug solubility. Suspensions of base and sulphate containing oleic acid but without co-solvent had unacceptable physical stability with rapid flocculation and settling or creaming. These were improved by inclusion of ethanol. Resultant stable suspensions of salbutamol sulphate formed a three-dimension flocculated network and the particle size, by laser diffraction analysis, was maintained in the desired range of 2–3 μm over 12 months real time and accelerated testing. In contrast, suspensions of salbutamol base in the HFA/ethanol system were physically unstable as a result of crystal growth and agglomeration.

This strategy has been employed in the HFA containing formulations of Airomir™ and Ventolin Evohaler™, where salbutamol is incorporated in suspension as the sulphate while CFC MDIs contained suspensions of salbutamol base.

### 2.7. The metering valve

The metering valve is required to retain and protect the contents of the canister while delivering a fixed volume (usually 25–100 μl) of the formulation accurately and reproducibly throughout use by the patient. Appropriate valve design and manufacture are critical to dose uniformity and require thorough investigation in the development of the product. The volume of the metering chamber and the concentration of drug substance determine the emitted dose from the valve.

At rest, the chamber is open to the bulk liquid within the canister. During actuation, the inner seal closes and outer opens so that only the contents of the chamber are discharged under the vapour pressure of the propellant.

The metering valve assembly is crimped onto the aluminium can containing the liquid fill and the seals around this junction and within the valve prevent leakage of the canister contents and ingress of moisture. Differences in performance of valves developed for CFC MDIs when exposed to HFA are principally due to the effect of propellant on the elastomeric components of the valve (Williams, 1995).

The solvency properties of the propellant affect the degree of swelling (or shrinkage) of valve elastomers and therefore valve function as a barrier to moisture ingress, release of volatile contents and reproducible dosing (Tiwari et al., 1998b). The emitted dose may be further influenced by sorption of drug to valve components or canister (June et al., 1994).

The water content of the formulation is critical to the solvency of the system and can destabilise both solution and suspension formulations. Hydrolysis of susceptible drugs and reduction in system vapour pressure due to ingress of water into the canister are further concerns. (Atkins et al., 1992).

HFA propellants have a higher capacity for water than CFCs and higher water transmission rates into HFA formulations are observed through valves developed for CFC MDIs (Williams and Tcherevatchenkoff, 1997). In a study of a model suspension formulation in HFA propellant using ethanol as co-solvent but without surfactant, the particle size (MMAD) increased with increasing water content in the formulation, although the size distribution (GSD) and percent respirable fraction were not affected (Williams et al., 1997).

The effects of varying ethanol concentration in placebo HFA-134a formulations on the performance of commercial metering valves containing different elastomeric components have also been reported (Tiwari et al., 1998b). Problems of valve sticking and continuous emission occurred in formulations containing no ethanol, but were reduced with inclusion of 2% v/v ethanol, and completely eliminated in solutions containing 10% v/v of ethanol, prompting the conclusion that ethanol lubricates the valve. This was at the expense of increasing leak rates and valve swelling with increasing ethanol content.

Nitrile based rubbers are the most commonly used elastomers in CFC MDI valve systems (Williams, 1995). In addition to the elastomer, compositions of these rubbers typically include filler and curing agents and they could also contain accelerators, activators/retarders, antioxidants, plasticiser, processing aids and colourants (Paskiet, 1997).

Table 6
Replacement of CFC containing MDIs with non-CFC alternatives (Official Journal of the European Communities, 1998)

| Product | Number of alternatives | Number of producers |
|---|---|---|
| *Category A: Short acting beta agonist brochodilators* | | |
| Salbutamol* | Two non-CFC salbutamol products | Two different producers |
| Terbutaline*, Clenbuterol, Fenoterol*, Bitolterol, Orciprenaline, Procaterol, Reproterol, Carbuterol, Hexoprenaline, Pirbuterol | CFCs for all category A products will no longer be considered essential once there are two available alternative salbutamol products produced by two different producers PLUS one other product defined as necessary under this strategy. Therefore, these two products will be replaced by a minimum of three CFC-free inhalers (two salbutamol + one other) | |
| *Category B: Inhaled steroids* | | |
| Beclomethasone* | Two non-CFC beclomethasone products | Two different producers |
| Dexamethasone, Flunisolide, Fluticasone*, Budesonide*, Triamcinolone | CFCs for all category B products will no longer be considered essential once there are available two alternative beclomethasone products produced by two different producers PLUS two other products containing different active substances defined as necessary under this strategy. Therefore these products will be replaced by a minimum of four CFC-free products (two beclomethasone + two others) | |
| *Category C: Non steroidal antiinflammatories* | | |
| Cromoglicic Acid*, Nedocromil* | CFCs for both category C products will no longer be considered essential once there is one alternative CFC product available to replace either of the two current products. Therefore, the two CFC products will be replaced by a minimum of one CFC-free product, except where both products are considered essential | |
| *Category D: Anticholinergic bronchodilators* | | |
| Ipratropium bromide Oxitropium bromide | CFCs for both category D products will no longer be considered essential once there is one alternative CFC product available to replace either of the two current products | |
| *Category E: Long acting beta agonist bronchodilators* | | |
| Salmeterol*, Formoterol* | CFCs for both category E products will no longer be considered essential once there is one alternative CFC product available to replace either of the two current products. Therefore, the 2 CFC products will be replaced by a minimum of one CFC-free product, except where both products are considered essential | |
| *Category F: Combination products* | | |
| | Combination products will be treated on a case by case basis. CFCs will no longer be considered essential once CFC products are available for each of the separate components in the combination | |

* Denotes products deemed necessary under this strategy in one or more member states.

ity of the active substance. Phase out of CFC products will be conducted in a two step process and the criteria are summarised in Table 6. When sufficient products containing a particular drug meet the defined criteria, the essential use exclusion will be removed and CFC will no longer be permitted for manufacture of MDI products of that drug. For example, for salbutamol (which accounts for 90% of the European short acting beta agonist market), the strategy stipulates the

Elastomer developments required for compatibility with HFA containing products have included; reduction in the content of elastomer in the device, improvements in the formulation of elastomers, reduction in components in the elastomer, use of alternative elastomer materials, removal of sources of polynuclear aromatics, avoidance of sulphur based curative processes and pre-cleaning /pre-extraction of elastomers (Howlett and Colwell, 1997).

The critical interdependence of MDI components to device functionality is evident in the preceding discussion and need to be fully considered in the design of the development programme, in order to achieve the desired performance characteristics in the reformulated product (Byron, 1992; Dalby et al., 1996).

## 3. Transition

The Parties to the Montreal Protocol required the preparation of national strategies for the transition to non-CFC containing MDIs by 31 January 1999. Continued availability of CFC for MDI manufacture is co-ordinated by the European Commission and the strategy for phase-out of CFCs in MDI was published in Official Journal of the European Communities in November 1998.

The stated principles guiding the phase out of CFCs in MDI are:

Principle 1: That all those involved will promote the transition to non-CFC alternatives.

Principle 2: That the health and safety of patients during the transition will be safeguarded.

Principle 3: That the nomination, approvals and licensing systems will be operated with efficiency, consistency and transparency.

The availability of CFC free products in the different member states may vary, dependent upon the national regulatory processes. The transition strategy for withdrawal of CFC based MDIs in the UK was published in 1999 by the Department of the Environment, Transport and the Regions. This attempts to co-ordinate the efforts of industry, health professionals and Government so that transition of patients to the new products is managed as effectively as possible.

When MDI products containing HFA propellants become available in European markets, the requirements for the 'essential use' exemption for CFC containing products will no longer be fulfilled. The European Commission has surveyed MDI manufacturers in order to predict the likely time course for CFC phase out. The best estimate is based around the intended dates of submission for Marketing Authorisations given by the producers (Table 5). It is envisaged that the transition to CFC-free MDI will be complete in the European Union by 2003. The UK strategy predicts completion of the transition one year earlier.

The strategies classify MDI products into the six categories based on the pharmacological activ-

Table 5
Expected time frame for loss of essential use status (Official Journal of the European Communities, 1998)

| Drug | First stated filing date | Last stated filing date | Likely loss of essential use status[a] |
|---|---|---|---|
| Salbutamol | 1994 | 2001 | 1998–1999 |
| Terbutaline | 2000 | 2004 | 2001–2002 |
| Fenoterol | 1998 | 2002 | 1999–2000 |
| Beclomethasone | 1996 | 2002 | 1999–2000 |
| Budesonide | 2000 | 2002 | 2001–2002 |
| Cromoglycate | 1998 | 1999 | 1999–2000 |
| Ipratropium bromide | 1999 | 2000 | 2000–2001 |

[a] Under the provisions of the strategy in all or some member states, provided that granting of Marketing Authorisations is not unduly delayed.

requirement for two alternative CFC-free products from different producers in an adequate range of doses. For products in categories C to E only one alternative is required. The next step occurs when sufficient drugs in a particular category are available, then essential use status will be removed for the entire category of products. The two systems will operate in parallel.

Categories A and B account for about 75% of CFC MDIs used in the UK and there are variety of brands and sources of active substance for the most widely used products. In category E, by contrast, salmeterol currently enjoys the exclusivity of new chemical entity and is marketed only by a single producer. At least one product in each of categories A to E, is also available as a dry powder inhaler.

The national strategy takes account of the prescribing preferences within the UK and considers the following drugs to be 'essential' so that phase out of CFC availability for particular categories will not be permitted until suitable non-CFC alternatives are available.

| | |
|---|---|
| Category A: | Salbutamol and terbutaline |
| Category B: | Beclomethasone, budesonide and fluticasone |
| Category C: | Sodium cromoglycate |
| Category D: | Ipratropium bromide |
| Category E: | Salmeterol |

Because of the prevalence of their use, at-least two different salbutamol products from different producers and one other CFC-free MDI containing terbutaline, must be available in an adequate range of doses prior to removal of essential status from category A. A similar situation arises with category B and beclomethasone dipropionate, but CFC-free MDIs containing fluticasone and budesonide are also required to be available prior to loss of essential status for this category.

Categories C, D and E require only one non-CFC product to be available and products stated to be essential in the UK in each of these categories are indicated above.

CFC use for combination products (category F) will no longer be considered essential once CFC free products containing each of the separate components, are available.

The strategy further stipulates requirements for production and distribution capacity of CFC-free MDIs, accommodation of distinct patient subgroups such as infants and the elderly, dose ranges to meet the needs of all patient groups and sufficient post marketing surveillance prior to removal of a particular essential use exemption.

It is notable that the only CFC-free BDP MDI currently licensed in the UK (Qvar™, 3M Healthcare), is not approved for use in children, although paediatric indications have been approved in other European Union countries.

Some products may not be reformulated or may lag the development of alternatives and patients using these products would be required to transfer to others within the same therapeutic category or to different delivery systems of the same drug, for example to a DPI.

It is envisaged that post marketing surveillance studies will take no more than 12 months from launch of a CFC-free MDI to highlight any safety issues and that the manufacture of further CFC-MDI, of that particular product, will be phased out over this time. This does not appear to take account of the different volume of use between different drug products and uptake by prescribers. During this time both CFC and CFC-free products would be available but it is acknowledged that availability of the original CFC products will vary greatly depending on stock rotation and it will require effective communication between prescribers, pharmacists and patients to ensure that the patient receives the intended product. Although it is acknowledged that CFC and CFC-free products are therapeutically equivalent, it is undesirable to switch back and forth between products containing the different propellants.

Withdrawal of essential use status for products or categories on fulfilment of these conditions will be administered by the European Commission, on advice from the competent authorities of Member states and other experts. This will, in turn be reflected in the subsequent European Commission application to the Parties to the Montreal protocol for CFCs to produce MDIs.

Manufacturers may continue to produce CFC MDI products within the UK (and Europe) for

export, particularly where there are significant cost implications for the developing world. The European Communication states that production for export will need to continue even after successful phase out in Europe but also that manufacturers should 'ensure that, wherever possible, patients relying on MDIs produced in Europe are given access to CFC-free inhalers and thereby benefit from the experience of transition in Europe'. One of the reasons given for the development of CFC-free MDIs was the threat of diminishing supply and increasing expense of CFC as essential use exemptions were removed and it is evident that this equally threatens the viability of manufacture of CFC MDIs for export only. This situation is currently being monitored by the Parties to the Montreal Protocol.

The success of this transition will be highly dependent on the awareness of healthcare professionals and patients of the issues of relevance to them and this is highlighted in both European and UK strategies. It is recognised that the level of awareness of healthcare professionals and patients about CFC-free MDIs is limited at present and that this will need to be improved as more become available in the marketplace. The development of active strategies to involve and inform patients will require involvement of Government, professional bodies, patient associations and manufacturers. Patients will notice differences in product appearance, taste, sound and impact in the oro-pharynx. They may be required to changeover to another drug or to a different delivery system or the dose of their usual drug may be changed. The potential for confusion is abundant but will be minimised by appropriate education and discussion with the users and it is recognised that this will also be an opportunity to revisit and reinforce information on good inhaler technique (Current Problems in Pharmacovigilance, 1999; Li Wan Po, 1999).

## 4. Re-formulated HFA-metered dose inhalers

CFC-free MDI products approved for marketing in the UK in September 1999 are listed in Table 7.

Devices containing salbutamol were, understandably, first to the market and Airomir™ (3M Healthcare, UK) was launched in the UK in 1995 followed by Ventolin Evohaler™(Allen and Hanburys, UK) in 1998. Beclomethasone dipropionate (BDP) was also launched in 1998 as Qvar (3M Healthcare, UK).

The approach to development of salbutamol and BDP was quite different. The template in the case of the salbutamol products was the in vitro aerodynamic profile of CFC salbutamol MDI and ultimately to demonstrate therapeutic equivalence to the CFC product in recognition of its 30 year history of safety and efficacy (Tansey, 1995). This clearly has the benefit that the patient can be changed over to the same dosage regimen. Although both HFA and CFC products are suspensions, the active is incorporated as the sulphate salt in reformulated products as compared to base in the original MDIs. The Airomir™ formulation

Table 7
HFA containing MDIs approved for marketing in the UK

| Product | Active | Excipients | Date of approval |
|---|---|---|---|
| Airomir™ (3M Healthcare) | Salbutamol sulphate (120 μg) | Oleic acid Ethanol HFA 134a | March 1995 |
| Airomir™Autohaler (3M Healthcare) | As above | As above | August 1997 |
| Qvar ™(and Autohaler) (3M Healthcare) | Beclomethasone dipropionate (50 μg, 100 μg) | HFA 134a Ethanol | June 1998 |
| Ventolin Evohaler™ (Allen & Hanburys) | Salbutamol sulphate (120 μg) | HFA 134a | July 1998 |

Table 8
Aerodynamic particle size of Qvar™ (3M Healthcare) and commercially available beclomethasone dipropionate CFC MDI (Leach et al., 1998)

| Product | MMAD (μm) | Fine particle fraction[a] (%) |
|---|---|---|
| Qvar ™(3M Healthcare) | 1.1 | 58 |
| Beclomethasone dipropionate CFC MDI | 3.5–4.0 | 21 |

[a] Less than 4.7 μm (Andersen Mark II Cascade Impactor).

contains oleic acid and overcomes problems of solvency in HFA-134a by inclusion of ethanol as a co-solvent. Ventolin-Evohaler™ contains only salbutamol sulphate suspended in HFA-134a without surfactant or co-solvent.

Development of Airomir™ has been well documented and it has been demonstrated to be equivalent to CFC salbutamol MDIs both in vitro and in the clinic (Tansey, 1997a,b).

The process of reformulation has also permitted some improvement to MDI performance. Variability in initial emitted doses of CFC MDIs has been reported, dependent on orientation and storage time (Cyr et al., 1991). The developments in valve technology required for Airomir™ show reproducible first dose after 14 days storage in any orientation (June and Ross, 1995). In practice, patients using intermittent 'reliever' MDI may titrate to effect, however it is clearly desirable to improve product dosing uniformity. CFC containing MDI also had problems reported with a 'tail off' effect where the dosing becomes erratic towards the end of the product life. Manufacturers routinely include fill volume overage so that dose delivery is reproducible over the 200 dose lifetime and the tail off effect occurs close to extinction, beyond the recommended 200 doses of the canister. The patient is not aware of the number of doses used or remaining because of the lack of a dose indicator. Developments in valve design required for Airomir™ showed reproducible dosing to extinction and a much more apparent end point for the patient (June and Ross, 1995). The benefit of a dose indicator for MDI remains unrealised.

Qvar™ was developed as a solution of BDP in HFA-134a and ethanol, in contrast to the original CFC containing products in which the same active was suspended in the propellant/excipient mixture. The drug formulation and developments in valve and actuator design have enabled reduction in the aerodynamic diameter of the Qvar™ aerosol and increase in the fine particle fraction (Tables 8 and 9). Data from one small in vitro study indicate that the aerosol emitted from the actuator is similar to that obtained using a spacer device (Table 9) (Purewal, 1998).

A small scintigraphic study of lung deposition of BDP in healthy volunteers demonstrated 55–60% deposition of the emitted dose from Qvar™ compared with only 4–7% for a formulation of CFC-BDP. Similar BDP deposition (56%) was

Table 9
Particle size distribution and fine particle mass of CFC-BDP (Becotide™ 100) and HFA-BDP (Qvar™) with and without a spacer, $n \geq 8$ (Purewal, 1998)

| Product | Emitted dose μg (SD) | Dose <5 μm μg (SD) | Dose <2.5 μm μg (SD) | Throat μg (SD) |
|---|---|---|---|---|
| CFC-BDP | 96.8 (4.0) | 22.0 (1.4) | 5.7 (0.7) | 58.3 (3.9) |
| CFC-BDP+spacer[a] | 51.8 (5.6) | 34.9 (3.5) | 7.7 (0.7) | 1.1 (0.3) |
| HFA-BDP | 77.2 (4.8) | 48.7 (4.5) | 44.6 (3.7) | 27.2 (4.5) |
| HFA-BDP +Autohaler[b] | 81.0 (3.7) | 51.6 (7.6) | 46.1 (5.8) | 27.8 (5.0) |
| HFA-BDP+spacer[c] | 48.8 (10.3) | 47.3 (10.2) | 42.7 (8.8) | 1.0(0.4) |

[a] Volumatic, Allen and Hanburys.
[b] Breath actuated inhaler, 3M Pharmaceuticals.
[c] Aerochamber, Trudell Medical.

also observed from the HFA-MDI in a further study in asthmatics (Leach et al., 1998). Increased lung deposition of the fine aerosol has permitted a dose reduction of 50% compared to CFC-BDP MDIs (Harrison et al., 1997) and therapeutic effect at half the corresponding dose of BDP CFC-MDI has been demonstrated in asthmatics (Davies et al., 1998). The lower administered dose would be expected to reduce inhaled steroid associated side effects such as hoarseness and cough. Adverse events associated with Qvar™ have been recently reviewed. (Davies, 1998; Shaw, 1999). High doses of BDP from Qvar™ (800 μg daily) have less suppressant action on hypothalamic-pituitary-adrenal function than equivalent BDP doses (1500 μg daily) from CFC-MDI. However, incidence of dysphonia and cough is not significantly different for those treated with Qvar™ compared with CFC-BDP. This is despite scintigraphic data, which show that the fractional deposition in the oro-pharynx is reduced from over 90% with CFC-BDP to about 30% with HFA-BDP (Leach, 1998).

Another HFA-134a reformulated BDP MDI, Beclazone™, Norton (Waterford, Eire) has been approved for marketing in some European Union countries. In contrast to Qvar™, this product is claimed to be therapeutically equivalent with CFC-BDP on a 1:1 dose basis (Milanowski et al., 1999). Beclazone™ is also a solution of the steroid in propellant but in vitro aerodynamic sizing data and scintigraphic deposition studies are currently not available in published literature.

Availability of different HFA-BDP products which are therapeutically equivalent at different dose schedules further complicates the transition process and the need for effective communication between health professionals and patients is further evident (Health Service Circular 1998/180).

## 5. Conclusion

In response to the ban on production of CFCs, aerosol manufacturers have sought environmentally acceptable replacement propellants to permit continued manufacture of MDIs. This is understandable given MDI popularity and the limited time-scales imposed by the Montreal Protocol.

HFAs provide a safe alternative to CFCs as propellants in these devices but their physicochemical properties have required extensive redevelopment of the entire product. This has improved the understanding of the interdependency of the various elements within the device and provoked debate on in vitro functionality testing and its relevance to clinical efficacy. Products developed thus far have provided benefits of improved drug delivery, dose uniformity and a patient discernible end point at canister extinction.

HFAs are not environmentally neutral and contribute to hydrocarbon emissions, global warming and acid rain. Nevertheless, the contribution of HFAs to environmental damage is considered to be comparatively small and the health benefit of drugs formulated using HFAs currently outweighs the environmental concerns, but this may not continue indefinitely.

The technical challenge to reformulate MDIs has almost been achieved and the next challenge is the transition of patients from CFC-MDIs to the new products. Professionals and public alike require information and education about the need for the transition and the implications for their treatment. Patients will be faced with unfamiliar products that look, taste, sound and feel different to their usual regimens. Some dosage schedules may be changed and some patients may be transferred to different active substances or to different drug delivery systems. Metered dose inhalers are used by many millions of patients and early identification of safety issues through effective pharmacovigilance is essential. Maintenance of disease control is paramount and the management of a seamless transition is the challenge for professionals, industry and Government.

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